A rationale for combining acetaminophen and NSAIDs for mild-to-moderate pain

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ABSTRACT

Analgesic therapy that combines indi - vidual agents with different mecha - nisms of action has potential advanta - ges for the management of mild-to-moderate pain in the outpatient setting. Theoretically, this approach can lead to greater efficacy and fewer adverse events. While the precise mechanism of action for the analgesic effect of aceta - minophen remains uncertain, accumu - lating evidence suggests that its acti - vity resides primarily in the central nervous system. In contrast, the site of action for the analgesic effect of nons - teroidal anti-inflammatory drugs (NSAIDs) is predominantly peripheral, within injured or inflamed tissue. Sev - eral controlled clinical studies among patients with musculoskeletal condi - tions, dental pain, or postoperative pain have shown that combinations of acetaminophen and NSAIDs provide additive pain-relieving activity, thereby leading to dose-sparing effects and im - proved safety. Further studies are war - ranted to determine the clinical utility and safety of acetaminophen/ NSAID combinations as analgesic therapy for common conditions associated with mild-to-moderate pain.

Current practice in managing mild-to-moderate pain

As a result of the growing emphasis on evidence-based medicine, treatment guidelines on pain management have acquired an increasingly influential role. The National Institutes of Health in 1987 was among the first to develop such guidelines on the broad issue of pain management (1). Since then, the World Health Organization (WHO), the American Geriatrics Society (AGS), the American College of Rheumatology (ACR), and the American Pain Society (APS) have generated similar documents that focus on specific pain states, such as cancer or arthritis (Table I) (2-5).

These documents vary in their emphasis on pharmacological vs. nonpharmcological modalities. Within the category of pharmacological therapy, however, the guidelines share the common feature of advocating a stepwise approach: They recommend safer and better-tolerated nonnarcotic analgesics as first-line agents, to be followed by more-potent narcotic analgesics as needed. Conspicuously absent from this logical stepwise approach are recommendations for the use of combinations of nonopioid analgesics that differ with respect to site of action (ie, peripheral [NSAIDs] vs central [acetaminophen]) prior to the use of narcotics. This approach is tacitly endorsed by researchers, in that acetaminophen is a standard "rescue medication" in many clinical trial protocols investigating the analgesic efficacy of NSAIDs (6-11).

It is time to examine the evidence in support of this rationale and conservative approach. This article will review studies on analgesic safety and efficacy in which a nonnarcotic centrally acting agent (acetaminophen) has been combined with a peripherally acting agent (an NSAID) for the treatment of mild-to-moderate pain associated with common medical conditions.

Targets for analgesic pharmacotherapy

Physicians generally take an empiric and pragmatic approach to the management of mild-to-moderate pain in outpatients. In most instances, these standard approaches are based on the pathophysiology of the pain state or the unique circumstances of the therapeutic encounter. For example, in situations in which the affective component of the pain response is especially prominent—for example, in the management of lacerations in the pediatric population—conscious sedation with a centrally acting agent such as ketamine may be indicated (12). Because prosta-

Table I. Guidelines for pain management.

	NIH Consensus Development Conference, 1987 (1)	World Health Organization, 1996 (2)	American Geriatrics Society, 1998 (3)	ACR Osteoarthritis Subcommittee, 2000 (4)	American Pain Society, 2002 (5)
Overall focus	Broad	Cancer pain	Common occurrence of pain due to multiple causes	Pain associated with osteoarthritis	Pain associated with osteoarthritis and rheumatoid arthritis
	Integrated approach that considers multidimensional aspects of pain	3-step analgesic ladder	Stepwise approach due to potential for side effects in elderly	Emphasis on improving function through education and non-pharmacologic treatment	Multiple treatment modalities considered in a stepwise approach
Patient types	All	Cancer patients	Geriatric patients	Osteoarthritis patients	Patients with osteoarthritis, rheumatoid arthritis, and juvenile chronic arthritis
Pain classification	Acute Chronic/malignant Chronic/non-malignant	Malignant	Nociceptive Neuropathic Mixed/indeterminate Psychologically based	Mild-to-moderate Moderate-to-severe	Mild-to-severe Neuropathic
Importance of non-pharmacologic strategies	Yes	No	Yes, for patients with chronic pain	Yes	Yes
Major concerns	Undermedication of malignant pain; overmedication of chronic, non-malignant pain	Need for specific goals	Pain management must be tailored for individual needs	Use of additional or alternative pharmacologic agents should be considered in the light of the risk of GI/renal toxicity	Importance of patient education, cognitive/behavioral strategies, nutritional considerations, and exercise, in addition to pharmacologic treatments
	Scheduled dosing preferred over PRN dosing	Scheduled dosing preferred over PRN dosing	Scheduled dosing preferred over PRN dosing	Scheduled dosing preferred over PRN dosing	Adverse events and costs associated with pharmacotherapy
	Need for better pediatric assessments	Evaluation of pain is a "vital first step"	Economic considerations needed to make balanced decisions on choice of intervention		

"PRN" indicates as needed.

glandins play a key role in the painful cramping associated with dysmenorrhea, physicians often prescribe NSAIDs, which inhibit cyclooxygenase (COX) (13). Nitrates help relieve pain associated with cardiac ischemia by virtue of venodilating, coronary artery dilating, and afterload-reducing effects (14).

Pain states commonly encountered in outpatient clinical care generally result from a nociceptive stimulus that triggers a sequence of neural events involving both the ascending and the descending pathways within the central nervous system. These signals culminate in an unpleasant sensation and an affective response. The ascending pathway transfers information from sensory nerves to higher brain centers—ie, the thalamus and cortex (15, 16). Endogenous opioids—endorphins, enkephalins, and dynorphins—are produced in the brainstem and are responsible for the processing of pain signals in the descending pathways (15-19). Melzack and Wall significantly extended and enhanced our understanding of the multiple factors influencing pain perception when they advanced the gate theory of pain. This theory highlights the critical influence of the central nervous system and, in particular, the dorsal horn of the spinal gray matter in inhibiting, promoting, and otherwise modulating pain perception (20, 21).

NSAIDs, cyclooxygenase, and prostaglandins

Prostaglandins play an important role in pain perception by sensitizing peripheral nociceptors (16, 22, 23). The critical first step in the generation of prostaglandins from arachidonic acid is catalyzed by the COX enzyme. The discovery in the 1980s of the two currently known isoenzymes—COX-1 and COX-2—paved the way for the development of selective COX-2 inhibitors (23-25). COX-1 is expressed under physiologic conditions to regulate normal cell function in various tissues, such as endothelium, gastrointestinal mucosa, kidneys, and platelets (26). COX-2 generally is not present in quiescent cells, but undergoes a dra-

matic increase in expression in endothelial cells, fibroblasts, or smooth muscle after induction by inflammatory mediators (26).

The primary mechanism of action of the NSAIDs is inhibition of COX, which leads to a decrease in the production of prostaglandins (27). NSAIDs are competitive inhibitors of COX, with the exception of aspirin, which irreversibly acetylates the enzyme, resulting in noncompetitive inhibition (26, 28). The analgesic activity of NSAIDs results from inhibition of COX-2, while their unintended adverse events stem primarily from inhibition of COX-1 (26). (One exception is the cardioprotective platelet-inhibiting effect of daily aspirin therapy, which results from COX-1 inhibition.)

The introduction of COX-2 inhibitors was associated with the promise of analgesic efficacy without the side effects associated with the nonspecific NSAIDs. Clinical trials with patients suffering from osteoarthritis have shown that the highly selective COX-2 inhibitors — celecoxib, rofecoxib, and valdecoxib — have efficacy comparable to that of the older, nonselective NSAIDs (29-31). Although highly selective COX-2 inhibitors have been shown to provide improved GI safety compared with traditional NSAIDs when assessed by hard clinical endpoints such as ulcer-related complications, data reported after these agents were introduced into clinical practice have raised doubt about the degree of GI protection afforded by COX-2—selective inhibitors (30, 31). Additional research is needed to demonstrate an improved safety profile for this class of analgesics (32).

NSAIDs versus acetaminophen: Different locus and mechanism of action

An accumulating body of evidence indicates that acetaminophen and NSAIDs produce analgesia by different mechanisms: NSAIDs act mainly in the periphery, whereas acetaminophen acts mainly in the brain and spinal cord (33-38). The exact mechanism of action of acetaminophen remains a mystery. Acetaminophen is a poor inhibitor of both COX-1 and COX-2 and is only weakly anti-inflammatory. This contributes to a more favorable safety profile relative to NSAIDs with respect to GI- and hemostasis-related adverse events (36, 39-41). Demonstration that the antipyretic activity of acetaminophen results from inhibition of COX in the brain led to speculation that analgesia also results from such inhibition within the central nervous system (34) and has prompted a search for additional, acetaminophen-sensitive COX isoforms (23, 39, 40, 42).

Ouellet and Percival demonstrated that the potency of acetaminophen against both COX-1 and COX-2 is increased 30-fold in the presence of glutathione peroxidase (which lowers tissue levels of peroxide) (43). The authors postulate the peroxide-sensitive inhibition of COX by acetaminophen correlates with tissue selectivity, insofar as peroxide levels are elevated in inflamed peripheral tissues but not in the brain during fever (44). Another study has shown that treatment of immune cells with diclofenac, a commonly prescribed NSAID, induces the expression of a form of COX with increased sensitivity to inhibition by acetaminophen and reduced sensitivity to other NSAIDs (45). Recently, acetaminophen's analgesic and antipyretic effects have been linked to inhibition of a putative "new" COX enzyme—COX-3 (39, 40, 42). Whether COX-3 merits description as a distinct COX isoform or is more accurately characterized as a slightly different version of COX-1 or COX-2 remains to be determined (23).

Arationale for combining analgesics

The use of analgesics over a period of days infrequently leads to complications; long-term use, however, can be associated with multiple problems (46), especially in special patient populations. Even over-the-counter (OTC) medications can be associated with serious events when used over a prolonged period of time or when taken inappropriately. Acetaminophen has been associated with hepatotoxicity when taken at doses above 7.5 to 10 g/day—2 to 2.5 times the maximum recommended daily dose of 4 g/day. Case report data suggest that there may be greater risk of hepatotoxicity when supratherapeutic doses are combined with alcohol consumption. A recent study by Kuffner and Dart, however, reported no evidence of significant liver injury in 102 alcoholic patients who, under controlled conditions, were given the maximum recommended daily acetaminophen dose of 4 g/day (1 g qid) for 2 days (47-49).

The elderly may be at particular risk for NSAID-related toxicity. Two weeks of continuous use of either an NSAID or a selective COX-2 inhibitor in the elderly can produce a measurable effect on renal function. This was recently demonstrated in a trial comparing the effects of diclofenac, rofecoxib, and amtolmetin guacyl in subjects between 60 and 80 years old with symptomatic osteoarthritis (50). Individuals taking diclofenac had a reduced glomerular filtration rate. Those in the rofecoxib group experienced sodium retention, with a significant increase in serum sodium, body weight, and blood pressure. Although amtolmetin guacyl, like diclofenac, is a nonselective NSAID, it did not impair renal function in this trial. The authors hypothesize that this renal-sparing effect may result from the stimulatory action of amtolmetin guacyl on inducible nitric oxide synthase, which may counterbalance the effects of COX inhibition within the kidney.

Chronic use of analgesics may lead to nephropathy (51,52). The risk of chronic renal disease associated with the use of NSAIDs increases 10-fold in men over 65 years of age (53), and the risk of NSAID-related GI complications increases 3-fold in patients over 60 years of age (54). For these reasons, acetaminophen continues to be the first-line agent for the management of mild-to-moderate osteoarthritis pain in this patient population (55, 56).

A carefully designed regimen that combines oral analgesics may offer multiple benefits for patients suffering from mild-to-moderate pain. Concurrent administration of acetaminophen to patients who require NSAIDs can provide greater analgesic efficacy with less risk of NSAID-related toxicity, thereby en-

abling a reduction in the NSAID dose (57,58). The combination of lower doses of multiple agents is an attractive strategy for maximizing the benefit-to-risk ratio of pharmacotherapy for pain. This approach is designed to avoid the dose-limiting adverse events of single-agent therapy (46, 57) and may be particularly applicable to elderly persons who suffer from chronic pain.

In addition, concomitant use of these agents is likely to result in additive efficacy, and possibly a synergistic effect, by providing analgesic activity at more than one level of pain signal— processing (59, 60). Although human clinical trials have not formally addressed the potential implications of synergistic analgesia, animal data suggest that acetaminophen exhibits antinociceptive synergy, both through coadministration with another agent and through "self-synergy" after 2-site administration (61, 62).

The evidence

Evidence regarding the analgesic effects achieved when acetaminophen is combined with NSAIDs has come from studies of experimentally induced pain as well as clinical studies of pain from osteoarthritis, dental surgery, and other surgical procedures (Table II).

Induced pain

In an animal model, acetaminophen was compared with 9 analgesics both as monotherapy and in combination (59). The combination of analgesics had an additive — and sometimes synergistic — effect. When acetaminophen and aspirin were administered together at half their usual dose, the combination was more active than either of the two drugs alone at the usual dose.

In a human experimental pain model involving thermally and electrically evoked stimuli, combination therapy with acetaminophen and tolmetin, an NSAID, produced additive analgesic effects on both pain threshold and pain tolerance (71). Although the authors note that these results are difficult to extrapolate to actual clinical pain states, the data suggest that such combination therapy has the potential to offer benefit in managing a broad range of pain states. Consistent findings emerge from another experimentally induced pain study of healthy male volunteers. In this study, the combination of naproxen and acetaminophen was found to be significantly superior to dipyrone in controlling pain produced by a pneumatic tourniquet ($P<0.05$) (72).

Osteoarthritis

In patients receiving naproxen (0.5 g/day) for relief of pain associated with osteoarthritis of the hip, the addition of acetaminophen (4 g/day) resulted in a significant ($P = 0.001$) reduction in overall pain and pain during movement or at rest versus treatment with naproxen alone (64). The analgesic effect of naproxen (0.5 g/day) combined with acetaminophen (4 g/day) was comparable to that obtained with a higher dose (1 g/day) of naproxen as a single agent, but was associated with a lower incidence of GI complaints. Similarly, combination therapy with acetaminophen and naproxen has been shown to shift the dose-response curve for naproxen to the left on measures of pain, joint index, and global effect in patients with rheumatoid arthritis, implying a dose-sparing effect (65).

Dental pain

A randomized double-blind study compared the analgesic effects of acetaminophen and of the NSAID diclofenac administered as either individual agents or as combination therapy for the treatment of acute pain associated with extraction of the third molar. Mean pain intensity during the 8-hour period after surgery was significantly decreased ($P=0.001$) in patients receiving acetaminophen (1 g) plus diclofenac (100 mg) relative to those receiving either agent alone (Fig. 1) (66). Interestingly, the addition of codeine (60 mg) to the acetaminophen/diclofenac combination did not significantly decrease mean pain intensity. The addition of codeine, however, was associated with a significant ($P = 0.037$) increase in adverse events (66). Another randomized, placebo-controlled trial of similar patients provides some additional, albeit limited, support. While there was no difference in pain relief between patients taking diclofenac with placebo and patients taking the combination of diclofenac and acetaminophen, those using the combination drug were much less likely to need rescue medications (67).

Surgical pain

Two types of surgical studies have been performed: those that examine the effect of pretreatment with combinations of drugs and those that examine the use of combination drugs postsurgically.

A randomized control trial of women undergoing elective abdominal/gynecological surgery examined pretreatment with acetaminophen, diclofenac, or their combination. Those receiving the combination were significantly less likely ($P< 0.01$) to need morphine during the first 6 to 24 hours after surgery (68).

Two trials of premedication in children have been conducted. In the first, the efficacy of rectal placebo or acetaminophen and ibuprofen alone or in combination as a pretreatment was examined (69). Children ages 1 to 6 who were undergoing same-day adenoidectomy received the drugs immediately after induction of anesthesia. The combination drug regimen was associated with a significantly lower need for rescue medication ($P<0.02$). In the second, the use of acetaminophen combined with a nonselective NSAID and a COX-2 inhibitor was examined (70). Children ages 3 to 15 were randomized to receive acetaminophen combined with placebo, ibuprofen, or rofecoxib before tonsillectomy. The need for supplemental analgesia postsurgically was then examined. Those taking the acetaminophen and ibuprofen combination required the least amount of supplemental medication. The time to supplementary medication for both the rofecoxib/acetaminophen combination and the placebo/acetaminophen combination was 62 minutes; for the ibuprofen/acetaminophen combination it was 156 minutes.

In a randomized placebo-controlled factorial-design trial of patients who had undergone various types of surgery—gynecologic, general, or orthopedic—the combination of acetamin-

ophen and the NSAID nalbuphine was significantly more effective in controlling pain than either drug alone (73). The addition of acetaminophen to nalbuphine did not increase the mild and transitory adverse effects reported with nalbuphine alone.

Self-medicating behavior

Patients who self-medicate for pain of various etiologies represent a source of additional information regarding usage patterns of acetaminophen/NSAID combinations. In a recent survey, 30% of patients with osteoarthritis reported concurrent usage of acetaminophen and either ibuprofen, naproxen, or diclofenac (74). Moreover, 70% of patients who took acetaminophen and 61% of patients who took ibuprofen claimed that they had obtained these medications as OTC products; only 24% of patients who took acetaminophen reported taking it under the advice of their physician (74). Although OTC medications that contain acetaminophen in combination with an NSAID (aspirin) are available, most also contain caffeine as an analgesic adjunct. Together with the clinical data summarized above, these results suggest the need for additional studies that assess the effectiveness of acetaminophen/NSAID combinations for pain control. Further studies are also needed to evaluate the effectiveness of acetaminophen/NSAID combinations for additional indications such as musculoskeletal injury, nonspecific "aches and pains" as a component of cold or flu symptoms, back pain, arthritis pain, tension headache, and cancer pain.

It must be recognized that acetaminophen/NSAID combination therapy has potential risks, particularly in patients who self-medicate. Physicians need to ask their patients who suffer from chronic pain about their use of OTC combination medications so that recommended doses of individual drugs are not exceeded (75). In addition, each individual agent has the potential to interact with other medication and, therefore, the potential to increase the risk of unwanted drug interactions in patients receiving polypharmacy. Thus, patient education plays an important role in

Table II. Beneficial effects of combining acetaminophen and NSAIDs for osteoarthritis, rheumatoid arthritis, and surgical pain

	Pain state	Centrally active agent and dose	NSAID and dose	Result
Schnitzer *et al.* 1999 (63)	Osteoarthritis (knee)	Tramadol (200 mg/day)	Naproxen (1000 mg/day) (initial dose)	78% reduction in daily dose of naproxen
Seideman *et al.* 1993 (64)	Osteoarthritis (hip)	Acetaminophen (4 g/day)	Naproxen (500 mg/day)	Combination equianalgesic with naproxen (1000 mg/day); reduction in GI complaints
Seideman 1993 (65)	Rheumatoid arthritis	Acetaminophen (4 g/day)	Naproxen (500, 1000, and 1500 mg/day)	Leftward shift in dose-response curves for pain, stiffness, and joint index after addition of acetaminophen
Breivik *et al.* 1999 (66)	Oral surgery (third molar)	Acetaminophen (1 g) with and without codeine 60 mg	Diclofenac 100 mg enteric-coated	Combination of diclofenac/acetaminophen with or without codeine was superior to either diclofenac or acetaminophen alone or the combination of acetaminophen and codeine alone
Matthews *et al.* 1984 (67)	Oral surgery (third molar)	Acetaminophen (500 mg)	Diclofenac sodium (50 mg)	Diclofenac/acetaminophen combination no more effective than diclofenac alone. However, only those taking combination did not need rescue medication
Montgomery *et al.* 1996 (68)	Surgery (elective abdominal gynecological)	Acetaminophen (1.5 g suppository)	Diclofenac (100 mg suppository)	Post-surgical morphine use lowest among those who took combination prophylactically
Viitanen *et al.* 2003 (69)	Surgery (pediatric adenoidectomy)	Acetaminophen (40 mg/kg suppository)	Ibuprofen (15 mg/kg suppository)	Combination did not improve post-operative analgesia, but did decrease the need for analgesia at home
Pickering *et al.* 2002 (70)	Surgery (pediatric tonsillectomy)	Acetaminophen (20 mg/kg)	Rofecoxib (0.625 mg/kg) Ibuprofen (5 mg/kg)	Combination of acetaminophen/ibuprofen effectively reduced the need for early analgesia (72% to 38%) when compared with acetaminophen/placebo. The combination of acetaminophen and rofecoxib did not (68% to 72%)

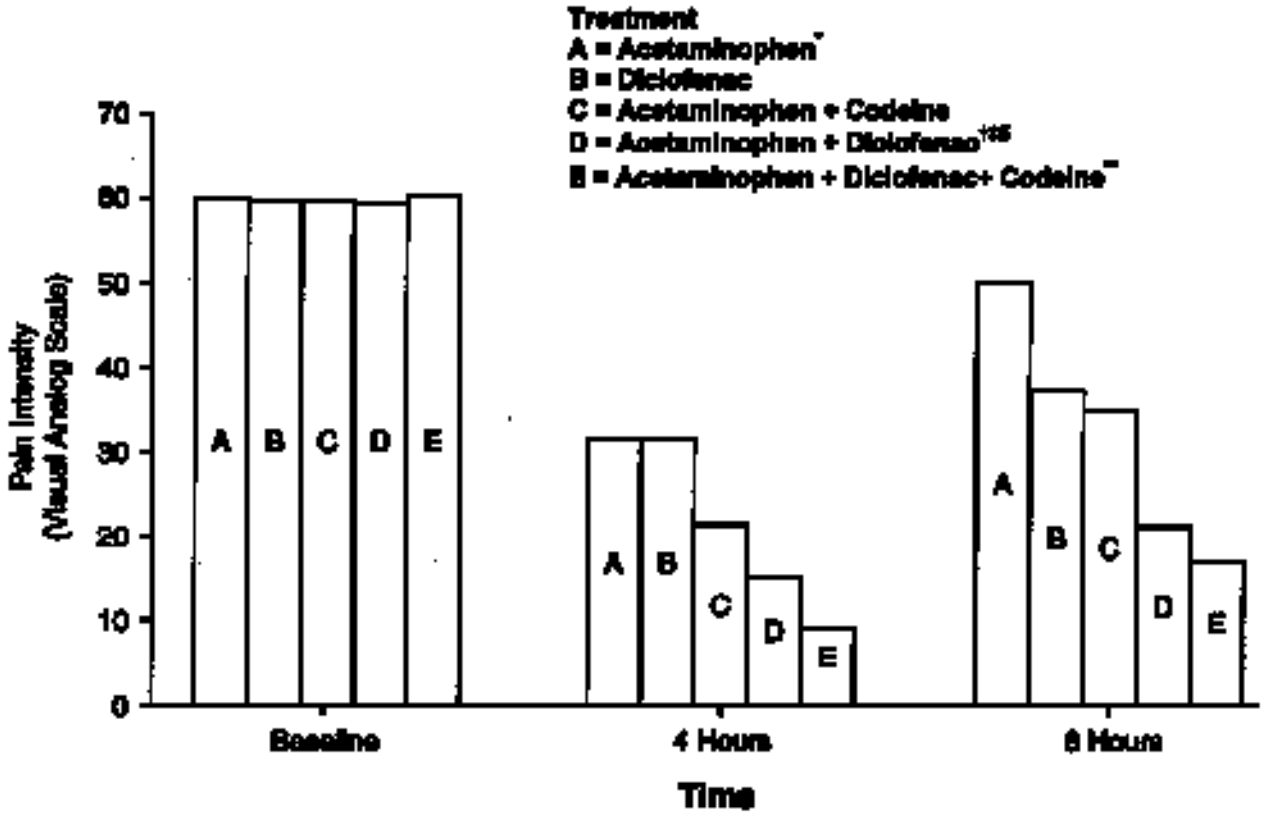

Fig. 1. Pain intensity scores on a visual analog scale at 4 hours and 8 hours after oral surgery. Patients were randomized to receive treatment with acetaminophen 1 g, diclofenac 100 mg, acetaminophen 1 g plus diclofenac 100 mg, acetaminophen 1 g plus codeine 60 mg, or acetaminophen 1 g plus diclofenac 100 mg plus codeine 60 mg after surgical removal of impacted third molars. Statistical analyses were conducted over the entire time period using a general linear model analysis.
* not significant vs diclofenac alone; † not significant vs acetaminophen plus codeine;(–) not significant vs acetaminophen plus codeine plus diclofenac; § P= 0.001 vs diclofenac alone or acetaminophen alone; ** P< 0.001 vs diclofenac alone or acetaminophen alone.
Adapted from Breivik *et al*. 1999 (65) with permission.

ensuring the safety of pharmacotherapy that involves multiple readily available agents. Additional studies are needed to address whether combining acetaminophen with NSAIDs poses additional risks, such as additive nephrotoxicity or hepatotoxicity. However, the previously mentioned survey data of people who combined acetaminophen and NSAIDs for self-medication of arthritis suggest that large numbers of patients are already combining these medications without apparent additive adverse effects (74).

Conclusions

The ACR guidelines recommend acetaminophen as initial therapy for osteoarthritis of the knee and hip. NSAIDs are recommended as alternative initial therapy in the patient with moderate-to-severe pain who also presents with inflammation (4). This review questions the rationale of this "either/or" approach to pain management for osteoarthritis. In studying the relevant medical literature, the following key findings emerge:

(1) NSAIDs and acetaminophen differ with respect to their analgesic mechanism of action.

(2) By virtue of their differing mechanisms of action, these agents may provide an additive analgesic effect.

(3) Available data from preclinical and clinical studies of experimentally induced pain, osteoarthritis, dental pain, and postoperative pain indicate that this form of combination therapy does indeed produce the desired additive effect.

(4) The evidence suggests that the combination of acetaminophen with an NSAID may provide enhanced analgesic efficacy with a dose-sparing effect for one or both of the medications.

(5) The dose-sparing effect has the potential to minimize the well-recognized risks associated with analgesic therapy for osteoarthritis, such as NSAID-induced gastropathy.

Additional research in this area may motivate re-evaluation of current recommendations, particularly if further research supports an NSAID-sparing effect for acetaminophen.

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